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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/269,573	07/16/1999	YOSHIHIDE HAYASHIZAKI	024705-083	1269

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EXAMINER
FORMAN, BETTY J

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 04/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/269,573	HAYASHIZAKI, YOSHIHIDE	
	Examiner	Art Unit	
	BJ Forman	1634	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 30 December 2002 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *30 December 2002*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☒ Applicant's reply has overcome the following rejection(s): *see Contintinuation of Advisory Action* .

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☐ The a)☐ affidavit, b)☐ exhibit, or c)☐ request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: *1-20,23,24 and 27-33*.

Claim(s) withdrawn from consideration: _____.

8.☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☒ Other: *Continuation of Advisory Action*

X Interview Summary of 18 Dec. 02

Continuation of Advisory Action

Continuation of 3:

The amendments overcome the new matter objections to the specification as they apply to Claims 1-22. The amendments overcome the rejections of Claims 1-22 under 35 U.S.C. 112, first paragraph, new matter. The amendments overcome the rejections of Claims 1-22 and 28-31 under 35 U.S.C. 112, second paragraph.

The previous new matter objection to the specification as they apply to Claims 32 and 33 are maintained. The previous rejections of Claims 32 and 33 under 35 U.S.C. 112, first paragraph, new matter are maintained. The previous rejections under 35 U.S.C. 102 (e), under 35 U.S.C. 102/103 and under 35 U.S.C. 103 are maintained.

Continuation of 7:

The amendments have been entered but the amendments do not place the claims in condition for allowance because the amendments do not overcome the rejections detailed above. Applicant's arguments are addressed below.

Regarding the rejection under 35 U.S.C. 102(e) as being anticipated by Chee et al

Applicant comments that the instant claims recite a hybridization step where a reference and target hybridize. Applicants argue that the reference sequence of Chee et al

does not hybridize with a target but instead Chee et al disclose the reference and target are the same sequence which are not complementary and therefore cannot hybridize. The arguments have been considered but are not found persuasive because contrary to Applicant's assertion, the claims are not drawn to hybridization between a reference and target. The instant claims are drawn to methods comprising a hybridization step wherein a full length cDNA selected from the group consisting of a) one or more nucleic acids fragments or b) one or more PNA fragments is hybridized with at least one fragment of which a mutation is to be assayed selected from the group consisting of a) one or more nucleic acids fragments or b) one or more PNA fragments. The claims do not recite a reference sequence or a target sequence and the claims do not define the claimed fragments as a reference or a target sequence.

Applicant points to Figure 6 of Chee to illustrate that their fragments are non-hybridizing sequences. Figure 6 has been review however, the figure does not illustrate the embodiment cited by the examiner which discloses the instantly claimed invention. While Figure 6 does illustrate the tiling method of Chee, the figure only illustrates the fragments on the substrate of Chee and not the fragments which are hybridized to the fragments. It is unclear why Applicant points to Figure 6 because the figure does not illustrate a hybridization method and therefore is not relevant to the claimed invention.

Applicant argues that the tiling of Chee et al is designed for target hybridization to short probes and not a reference sequence. Applicant further argues that the instant invention requires hybridization and only requires one full-length cDNA in order to detect a gene of interest. The argument has been considered but is not found persuasive because the instant claims are drawn to hybridization step wherein a full length cDNA selected from the group consisting of a) one or more nucleic acids fragments or b) one or more PNA fragments. As such, the claims define the full length cDNA as one or more fragments. Therefore, the tiled probes of Chee et al are encompassed by the instantly claimed one or more fragments because the fragments of Chee et al have the full length cDNA.

Regarding the rejection under 35 U.S.C. 102/103 as being anticipated or in the alternative obvious over Wagner et al.

Applicant argues that Wagner et al and Wagner using the methods of Sambrook do not disclose preparation of full-length cDNAs but instead teach preparation of ESTs. The argument has been considered but is not found persuasive because Sambrook, as cited in the Office Action, teach preparation of cDNAs and because Sambrook never teaches or discusses preparation of ESTs. Additionally, Applicant has not pointed to a passage in the teaching of Sambrook or Wagner wherein ESTs or their preparation are discussed. Furthermore, the claims are drawn to a full length cDNA wherein the cDNA is defined as being selected from the group consisting of a) one or more nucleic acids fragments or b) one or more PNA fragments. Therefore, even if the cDNAs of Wagner et al and/or Sambrook were fragments e.g. ESTs, the fragments of Wagner et al and/or Sambrook are encompassed by the instantly claimed cDNAs.

Applicant comments that the Office Action states that Sambrook does not disclose preparation of full-length cDNAs. The passage cited by Applicant is presented below. It is noted that the passage does **not** state that Sambrook does not disclose preparation of full-length cDNAs as Applicant asserts. Therefore, Applicant's arguments misrepresent the examiner's position. As such, the arguments are not relevant to the rejection.

> The preceding rejection is based on judicial precedent following In re Fitzgerald, 205 USPQ 594 because Wagner et at. is silent with regard to the hybridization partner having all of a sequence of a full-length gene. However, the sequence of a full-length gene recited in Claim 1 is deemed to be encompassed in the cDNA hybridization partner of Wagner et a1. because Wagner's cDNAs are prepared using the method of Sambrook who specifically and repeatedly teach preparation of long cDNA. Alternatively, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the teaching of Sambrook et al to the cDNA preparation of Wagner et

al and to analyze the cDNAs prepared and to specifically select and immobilize cDNAs having the full-length sequence as taught by Sambrook for the obvious benefits of analyzing the complete sequence for mutations. (exact copy of, page 10, last paragraph from the Office Action of Paper No. 27).

Applicant argues that it would not have been obvious to apply the teaching of Sambrook to Wagner and to prepare full-length cDNAs because "Even now, full-length cDNA were difficult to obtain." The argument has been considered but is not found persuasive because the instant specification (page 5) teaches that full length cDNAs were well known, methods for preparing full length cDNA were well known and methods of fixing full length cDNAs onto a substrate were well known. Therefore, Applicant's are not convincing because the arguments contradict the teaching of the specification.

An article comprising a substrate on which DNA fragments are fixed has been known as, for example, a DNA chip. **Microarray chips on which cDNA are fixed, and methods for measuring expression levels of transcription products utilizing them have already been known.** The method of the present invention is characterized in that it simultaneously detects expression levels of transcription products, which are detected by the microgram chip, and expression levels of the mismatched base pairs, which cannot be detected by the measurement method utilizing the microgram chip. As will be described hereinafter, information of the both can be obtained simultaneously by measuring the expression level of mismatched base pairs with a signal different com the signals for measuring expression levels of transcription products.

More specifically, the nucleic acid material to be fixed on the substrate may be, for example, **full length cDNA, EST (part of cDNA), genome DNA or the like, and they can be prepared by using known methods.** Examples of the genome DNA include plasmid, phages, PAC, BAC, YAC and the like.

The aforementioned full length cDNA, EST, genome DNA and the like can be cut out and bed on the substrate by a known method. (exact copy of the specification, page 5, lines 10-28).

Applicant argues that the examiner has improperly placed the burden on Applicant to provide evidence that the instantly claimed cDNAs are either different from or non-obvious over Wagner and/or Sambrook because the examiner bears the burden of factually supporting a prima facie conclusion of obviousness . The argument has been considered but is not found persuasive because the examiner has provided factually supporting evidence of obviousness as detailed in the Office Action and discussed above.

Regarding the rejections under 35 U.S.C. 103 as being obvious over Wagner et al. in view of Zoltukhin; in view of Gifford; in view of Chirildian; and in view of Zoltukhin and Fleck

Applicant argues that the method of Wagner utilizes tiling and requires several oligonucleotides in contrast to the instant invention which uses full length cDNAs and requires only one cDNA to detect a mutation. Applicant further argues that the skilled artisan would not thing that the disclosure of Wagner includes full length cDNA and provides no motivation to provide full length cDNAs. The argument has been considered but is not found persuasive because as stated above, the claims are drawn to a full length cDNA wherein the cDNA is defined as being selected from the group consisting of a) one or more nucleic acids fragments or b) one or more PNA fragments. Wagner teaches their method wherein the fragments fixed on the substrate (i.e. hybridization partner) are cDNA (page 13, lines 6-9, Example 111 and Claim 3) and is prepared by method according to the methods of Sambrook (Example 111, page 44, lines 27-31). Sambrook teaches method for preparing CDNA (pages 8.53-8.8 1) and they specifically and repeatedly teach preparing long cDNAs to thereby create a complete CDNA library (see page 8.54 (3), check size of product; page 8.6 1(ii), longest CDNA are desired; page 8.64 (5), first strand of cDNA should range in size of 300 bases to 5kb, with majority between 1 and 2 kb; pages 8.70-8.72, a complete section teaching size Selection of cDNA; page 8.76 (2) analysis of cDNAs to obtain cDNA greater than 1kb; and page 8.80-8.8 1 this section teaches methods of overcoming CDNA synthesis problems e.g. incomplete cDNA). As such, the

teaching of Wagner and Sambrook clearly teach and suggest the instantly claimed method comprising cDNAs.

Applicant argues that the preparation of full length cDNAs requires particular skill and methods and at the time the invention was filed and even today, it is difficult to obtain full length cDNAs. Applicant further argues that the teaching of Wagner is not enabling for the preparation of full length cDNAs. The arguments have been considered but are not found persuasive because, as stated above, the instant specification (page 5, as presented above) teaches that full length cDNAs were well known; methods for preparing full length cDNA were well known; and methods of fixing full length cDNAs onto a substrate were well known. Therefore, Applicant's are not convincing because the arguments contradict the teaching of the specification.

Applicant further argues that the teachings of the secondary references fail to overcome the deficiencies of Wagner. The arguments are not found persuasive for the reasons stated above regarding Wagner.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:30 TO 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BJ Forman, Ph.D.
Patent Examiner
Art Unit: 1634
April 10, 2003